Phenotype-genotype correlation in a series of 131 patients studied for calcium-sensing receptor gene (CASR)

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INTRODUCTION

CASR loss-of-function mutations lead to

- familial hypocalciuric hypercalcemia (FHH)
- neonatal severe hyperparathyroidism
- and primary hyperparathyroidism.

FHH is characterized by mild hypercalcemia, hypocalciuria, calcium clearance/creatinine clearance (CaCl/CrCl)<0.01, normal or high PTH level. Nevertheless the phenotype may vary (Thakker 2012).

The aim of this work was to compare the phenotypes of patients bearing or not a pathogenic CASR-mutation.

METHODS

Patients included (n=131; 96 female, median(IQR) age 63(40-77))
referred for a calcium disorder not explained by sporadic hyperparathyroidism,
were sequenced for *CASR* gene after written informed consent.

Patients taking diuretics, diphosphonates, lithium, with kidney failure, CaSR-antibodies or gain-of-function *CASR*-mutations had been excluded.
A healthy group of control patients from Pneumology Department was compared to patients with calcemia disease.

Gender, age, nephrolithiasis, bone absorptiometry, blood calcium, phosphate, creatinine, 25-hydroxyvitaminD and PTH levels, 24-H calciuria, and CaCl/CrCl were compared according to the level of calcemia <100, 100-105 or >105 mg/L and the presence of a pathogenic CASR mutation.

RESULTS

The CASR-mutated group (n= 21) showed higher calcemia and lower PTH levels than the non-mutated group (n=110), with no difference for other parameters (Table 1).

The non-mutated group included 51 normal CASR, 50 heterozygous and 9 homozygous or composite heterozygous variants. The comparison of these 3 sub-groups with the CASR-mutated group also differed for calcemia and PTH (p=0.01) (Table 2).

CaSR-mutations and CASR-variants were identified respectively in none and 15 (53%) of the 28 patients with calcemia<100mg/L, 4 (14%) and 14 (50%) of the 28 patients with calcemia between 100-105mg/L, and 17 (22%) and 30 (40%) of the 75 patients with calcemia>105mg/L (Table 3).

Seven of 13 (53%) patients tested without any calcium disorder bore CASR-variants.

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Table 1: Comparison of biological parameters between mutated and non-mutated groups

	Non mutated N=110	Mutated N=21	p
Ca (mg/L)	105(98-111)	108(105-116)	**0.01**
PTH (pg/mL)	83(52-107)	50(32-91)	**0.03**
25OHvitD(ng/mL)	23(15-33)	27(21-35)	0.20
CaU(mg/24h)	123(65-188)	120(45-183)	0.74
CaCl/CrCL	0.01(0.01-0.02)	0.01(0-0.02)	0.27

Table 2: Biochemical parameters according to genotype

	Normal N=51	Hétérozygous Variant N=50	Homozygous or heterozygous composite variant N=9	Mutated	p
Ca (mg/L)	106(98-109)	102(98-110)	115(110-117)	108(105-116)	**0.01**
CaCl/CrCl	0.01(0.01- 0.03)	0.01(0.01-0.02)	0.01(0- 0.02)	0.01(0- 0.02)	0.0571
PTH (pg/mL)	91(52-133)	74(38-96)	85(64-146)	88(32-91)	**0.0188**
25OHvitD (ng/mL)	23(14-32)	23(15-32)	27(20-35)	27(21-35)	0.5473
Ca/PTH	1.2(0.8- 2)	1.4(1-2.8)	1.2(0.8-1.8)	2(1-3)	0.0078

Table 3: Genotype according to blood calcium level

	Normal	Hétérozygous variant	Homozygous or heterozygous composite variant	Mutated	p
Healthy and Ca<100mg/L	47%	45%	8%	0	0.14
Ca< 100mg/L and calcium disorder	47%	46%	7%	0	
Ca 100-105 mg/L	36%	50%	0	14%	
Ca>105	37%	30%	9%	23%	

CONCLUSION

**50% of patients with calcemia<105mg/L showed a CASR-variant,
whereas 40% with calcemia>105mg/L showed a CASR-mutation,
with lower PTH levels, but no difference in terms of calciuria or (CaCl/CrCl) despite similar vitaminD status.
Calcemia/PTH ratio>2 could be a better marker of pathogenic CASR-mutation than (CaCl/CrCl)<0.01**

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